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REVIEW

The future of hybrid imaging—part 1: hybrid imaging technologies and SPECT/CT

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Abstract Since the 1990s, hybrid imaging by means of software and hardware image fusion alike allows the intrinsic combination of functional and anatomical image information. This review summarises in three parts the state-of-the-art of dual-technique imaging, with a focus on clinical applications. We will attempt to highlight selected areas of potential improvement of combined imaging technologies and new applications. In this first part, we briefly review the origins of hybrid imaging and comment on the status and future development of single photon emission tomography (SPECT)/computed tomography (CT). In short, we could predict that, within 10 years, we may see all existing dual-technique imaging systems, including SPECT/CT, in clinical routine use worldwide. SPECT/CT, in particular, may evolve into a whole-body imaging technique with supplementary use in dosimetry applications.

Keywords Hybrid imaging · SPECT · CT · SPECT/CT · PET/CT · PET/MR

"The world is greater than the sum of its parts" (Aristotle 384–322 BC).

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Introduction

For centuries, medical imaging has been invasive and potentially harmful to the body of the patient (Fig. 1). Frequently, diseases were missed or diagnosed too late because external anatomical changes were observed long after the onset of disease. During the past century, technologies have progressed rapidly and have had an impact on medicine to an extent unseen before. One of the most cited observations that led to the development of an entirely new medical discipline was the discovery of X-rays by Wilhelm Conrad Roentgen in 1895 [1]. The first applications of X-rays were not necessarily medical, let alone clinical, and it took a few years before the full scope of X-ray imaging was explored for the benefit of the patient.

The early 1970s saw the introduction of the first X-ray computed tomography (CT) system, initially for brain imaging and then later for whole-body studies [1]. Following CT, the 1980s witnessed the appearance of clinical magnetic resonance (MR), a technique of particular importance for imaging patients because it does not require the use of ionising radiation. These two techniques, CT and MR, located within radiology departments, came to dominate the imaging of human anatomy. However, in diagnosing and staging disease or monitoring response to therapy, anatomical imaging does not always provide the complete picture. Functional or metabolic changes may

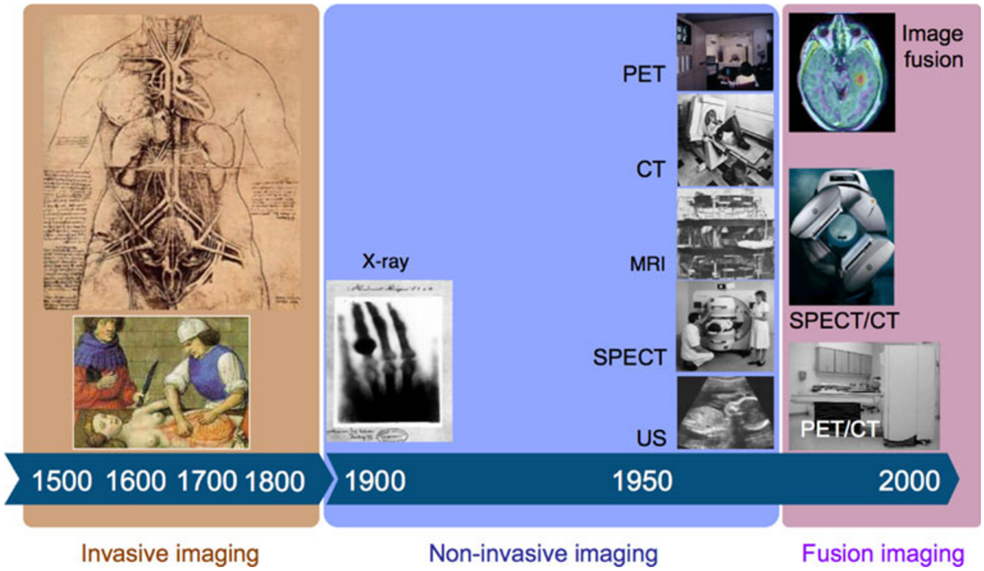

Fig. 1 From invasive to non-invasive imaging. It took more than 500 years to establish non-invasive imaging from the pencil drawings of Da Vinci to routine tomographic imaging. Fifty years were needed to introduce hybrid imaging. With the availability of stand-alone anatomical and functional imaging, the first attempts to fuse separately acquired images were made as early as the 1960s. Computer-assisted software fusion can be regarded as a main incubator of hardware fusion, first introduced in the late 1980s, a decade before prototype hardware-fusion became available

occur, even in the absence of a corresponding anatomical correlate.

Nuclear medicine techniques, initiated in the late 1940s, image functional processes by using radioactive tracers and photon detectors. Tomographic imaging with radionuclides actually predates CT, with early attempts dating from 1963 [2]. The first human tomographic images with positron-emitting isotopes were presented in 1972 [3], thus establishing positron emission tomography (PET) on the map of medical imaging technologies, to be joined by single photon emission tomography (SPECT) a year or so later, following on from the pioneering work of the early 1960s [4].

Various methods of imaging have become available over the past century that have made patient observation, disease diagnosis and therapy follow-up feasible, and above all non-invasive. We know that disease originates from physical distress as well as from changes on the molecular and physiological level. In most cases of serious diseases, early diagnosis is key and, therefore, imaging the anatomy of a patient may not suffice in making a correct and timely diagnosis. Therefore, medical doctors typically employ a combination of imaging techniques during the course of diagnosis and subsequent treatment to monitor their patients. In other words, both functional and anatomical information are essential in state-of-the-art patient management. An appreciation for this type of combined information is best illustrated with the introduction of the term “anato-metabolic imaging” [5], in reference to an imaging technique that gathers both anatomical and functional information, ideally within the same examination.

The advantages of integrated, anato-metabolic imaging are manifold [6]. First, a single examination would provide comprehensive information on the state of a disease. Here, functional, and thus, less anatomically accurate information would be gathered and displayed in a widely appreciated anatomical context. Second, patients would be invited for only one, instead of two or multiple examinations. Third, while engineering costs for combined imaging devices may initially be high, customers would benefit from purchasing a single device rather than two independent devices. Fourth, as we will see later on, the combination of complementary imaging techniques can yield synergy effects for the acquisition and processing of image data. Fifth, experts in radiology and nuclear medicine are hopefully forced to discuss and integrate their knowledge into one report.

While each of the above points can be debated, it is generally assumed that combined imaging has revolutionised imaging and medical diagnosis. Nonetheless, while technological innovation always partners enthusiasm and public interest, subsequent devices and imaging techniques must be affordable and assessed for their health benefit to justify their introduction into a public healthcare system [7]. Unfortunately, today, over 10 years after the introduction of the first commercial dual-technique imaging systems, technology assessment and cost-benefit analyses are not applied to the same standards across imaging techniques.

Here, we intend to describe briefly the status of combined imaging and, based on recent developments, hypothesise on the short-term future of dual- and multi-technique imaging. Further, we will highlight requirements for supporting a wider dissemination of hybrid imaging.

Hybrid imaging technologies

Historically, medical devices to image either anatomical structure or functional processes have developed along somewhat independent paths. The recognition that combining images from different techniques can nevertheless offer significant diagnostic advantages gave rise to sophisticated software techniques to co-register structure and function retrospectively [8, 9]. The usefulness of combining anatomical and functional planar images was evident to physicians as early as the 1960s [2]. In addition to simple visual alignment, or the use of stereotactic frames that are undesirable or inconvenient for diagnostic imaging, sophisticated image fusion software was developed from the late 1980s onwards. For relatively rigid objects such as the brain, software can successfully align images from MR, CT and PET, whereas in more flexible environments, such as the rest of the body, accurate alignment is difficult owing to the large number of possible degrees of freedom.

Alternatives to software-based fusion have now become available through instrumentation that combines two complementary imaging techniques within a single gantry, an approach that has since been termed "hardware fusion" (Fig. 2). A combined, or hybrid, tomograph such as SPECT/CT or PET/CT can acquire co-registered structural and functional information within a single study. The data are complementary allowing CT to accurately localise functional abnormalities and SPECT or PET to highlight areas of abnormal metabolism.

As a result, following their introduction into the clinic, combined PET/CT and SPECT/CT devices are now playing an increasingly important role in the diagnosis and staging of human disease. Recently, the first clinical PET/MR prototype systems have started to undergo clinical evaluation and, furthermore, other imaging combinations are being discussed.

SPECT/CT

Background and reasoning

In 1996, Blankespoor and co-workers presented a combined SPECT/CT design comprising a clinical SPECT gamma camera in tandem with a clinical single-slice CT [10]. The images were co-registered by taking into account the axial displacement between the CT and SPECT imaging fields. After injection of the radiotracer and an uptake period, the patient was imaged first with CT and subsequently with SPECT. The CT data were used to generate the SPECT attenuation correction factors [11]. The combined device was used to perform a small number of clinical studies, such as for quantitative estimation of radiation dosimetry in brain tumour patients [12].

Since then, SPECT/CT has advanced rapidly and several commercial system designs are available today (Fig. 3). The Infinia Hawkeye series (GE Healthcare) has remained a viable option for SPECT imaging combined with low resolution anatomy [13, 14]. The latest design, the Infinia Hawkeye 4, features a four-row detector unit with a rotation speed of 23 s. An axial field of 40 is now acquired in about 3–4 min. Apart from their obvious role in localisation, the anatomical images can be used to generate attenuation correction factors. This is more advantageous for SPECT

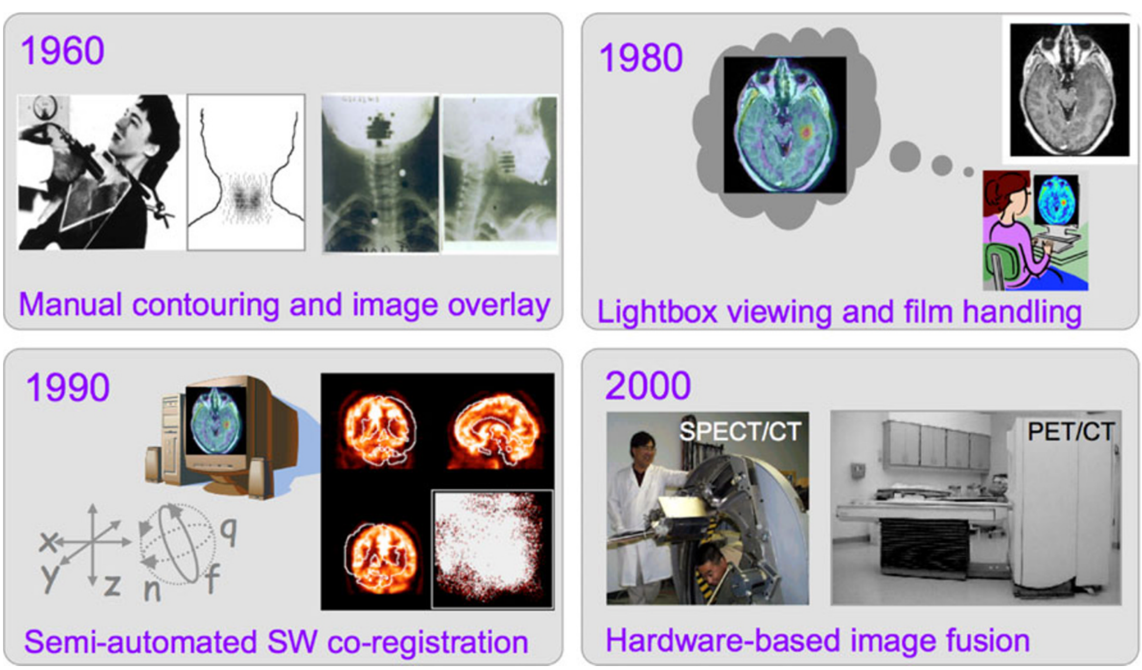

Fig. 2 Attempts to combine anatomical and functional image information in clinical routine from 1960 to 2000

	Discovery NM/CT 670 GEHC	Anyscan Mediso	Brightview-XCT Philips	Symbia Siemens
SPECT Axial FOV	40 cm	39 cm	41 cm	39 cm
SPECT Transv FOV	54 cm	53 cm	54 cm	53 cm
CT slices	16	16	cone beam	2, 6, 16
Max. coverage	20 mm	20 mm	140 mm	19 mm
CT tube power	50 kW	60 kW	10 kW	50 kW
CT tube max.voltage	140 kVp	140 kVp	120 kVp	130 kVp
CT tube max. current	440mA	500 mA	80 mA	345mA
Max. CT rotation	0.5 s	0.4 s	12 s	0.5 s
Min. CT slice width	0.625 mm	0.6 mm	0.3 mm	0.6 mm

Fig. 3 Selected state-of-the-art SPECT/CT systems. Since the introduction of the first commercial SPECT/CT system employing a dual-head SPECT and a low-dose, single-slice CT-like transmission source in 1999, SPECT/CT has advanced towards a hardware combination of multiple SPECT detector heads and spiral CT systems

than for PET because the SPECT attenuation correction factors depend on the (unknown) depths in tissue of the detected photons (Fig. 4).

In 2004 the first combined clinical SPECT/CT system, the Symbia T2 (Siemens Medical Solutions), was launched comprising a dual-slice Emotion CT and a dual-head Symbia S scintillation camera. This is the first commercial design that incorporated a fully-clinical CT system. This design, now named the Symbia TruePoint SPECT/CT, is also available with 6-slice and 16-slice Emotion CT systems. Philips Healthcare now offers a high-performance SPECT/CT with their Precedence platform. The design is available with a 16-slice CT that has a minimum rotation time of 0.4 s. Similarly, GE Healthcare added a SPECT/CT to their product portfolio. The NM/CT 670 combines a SPECT system with a 16-slice BrightSpeed Elite with 0.5 s rotation time. Finally, Hungary-based Mediso company offers a SPECT system that can be combined with CT (and even PET). The CT is a 16-slice spiral system. A trend seen from Fig. 3 is the combination of state-of-the-art SPECT detector heads with mid-tier clinical CT, a combination that was previously described as potentially more useful than combining CT and PET [15].

Main applications

The Hawkeye has experienced increasing popularity for SPECT where even low-resolution anatomy can have a significant impact on image interpretation. Numerous studies performed on Hawkeye systems have confirmed the utility of co-registered anatomical information for the interpretation of SPECT images [13, 16].

The introduction of SPECT/CT in 2004 offers physicians the additional choice of a fully clinical CT study aligned with the SPECT study. SPECT imaging has access to a much wider range of clinically established biomarkers and radiopharmaceuticals than clinical PET, which, today, is limited mainly to [^{18}F]FDG (FDG) for glucose utilisation and ^{82}Rb for cardiac perfusion studies. The fusion of CT and SPECT images from stand-alone systems has already demonstrated clinical utility [17]. Thus, hardware fusion of SPECT with a 16-slice CT offers interesting further

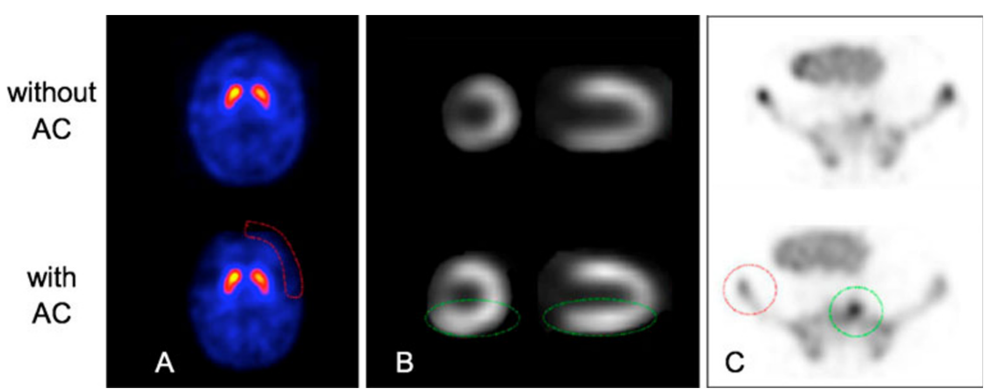

Fig. 4 With the introduction of SPECT/CT, attenuation correction has been made routinely available to SPECT, and, therefore, helped to improve image and diagnostic quality of the SPECT for a variety of applications: (**a**) brain, (**b**) cardiac and (**c**) skeletal imaging. (Adapted from Buck et al. [16])

possibilities for cardiac SPECT. The combination of calcium scoring from CT and a cardiac SPECT study with ^{201}Tl for tissue viability and ^{99m}Tc-sestamibi for perfusion is an attractive possibility.

Some of the SPECT tracers are highly specific to the disease process and the corresponding images offer little or no anatomical information compared with an FDG whole-body study. Examples of such specific biomarkers include ^{123}I and ^{131}I for metastatic thyroid disease and ^{131}I-labelled cholesterol for adrenal studies. SPECT/CT can also play an important role in imaging benign and malignant bone disease most commonly with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) to distinguish foci of increased metabolism [18], and neuro-endocrine tumour imaging with ^{111}In-octreotide, ^{111}In-pentetreotide or ^{123}I-MIBG where uptake can be highly tumour-specific and impossible to localise anatomically without the co-registered CT [16, 19]. In bone imaging, for example, combined SPECT/CT may improve diagnostic accuracy compared with SPECT only [20, 21] and help distinguish between osteomyelitis, aseptic necrosis and metastatic disease. As with PET/CT, SPECT/CT has been shown to be beneficial in recurrent head and neck cancer imaged with ^{123}I-IMT {L-3[^{123}I]-iodo-alpha-methyl tyrosine (IMT)-SPECT}. The accuracy of sentinel node mapping is improved by accurately localising the affected nodes (Fig. 5). The co-registered CT should also improve the diagnostic accuracy of ^{111}In-capromab pendetide (ProstaScint) imaging for prostate cancer, a disease for which FDG-PET is of questionable value although other PET biomarkers not yet clinically available show some promise. Finally, myocardial perfusion scintigraphy by SPECT is one of the most widely used and well established non-invasive tools for the diagnosis of ischaemic heart disease with a documented high diagnostic accuracy [22]. The first promising results with ^{82}Rb-PET perfusion imaging [23] notwithstanding, combined SPECT/CT imaging can provide such unique complementary information on coronary anatomy as well as on pathophysiological lesion severity, which improves diagnostic assessment and risk stratification and helps make decisions with respect to revascularisation in patients with coronary artery disease. Furthermore, SPECT/CT helps to overcome heterogeneous photon attenuation in the thorax—one of the most notable limitations of myocardial perfusion scintigraphy. The integration of CT data for attenuation correction (Fig. 4) supports clinically relevant improvements in diagnostic testing [24, 25].

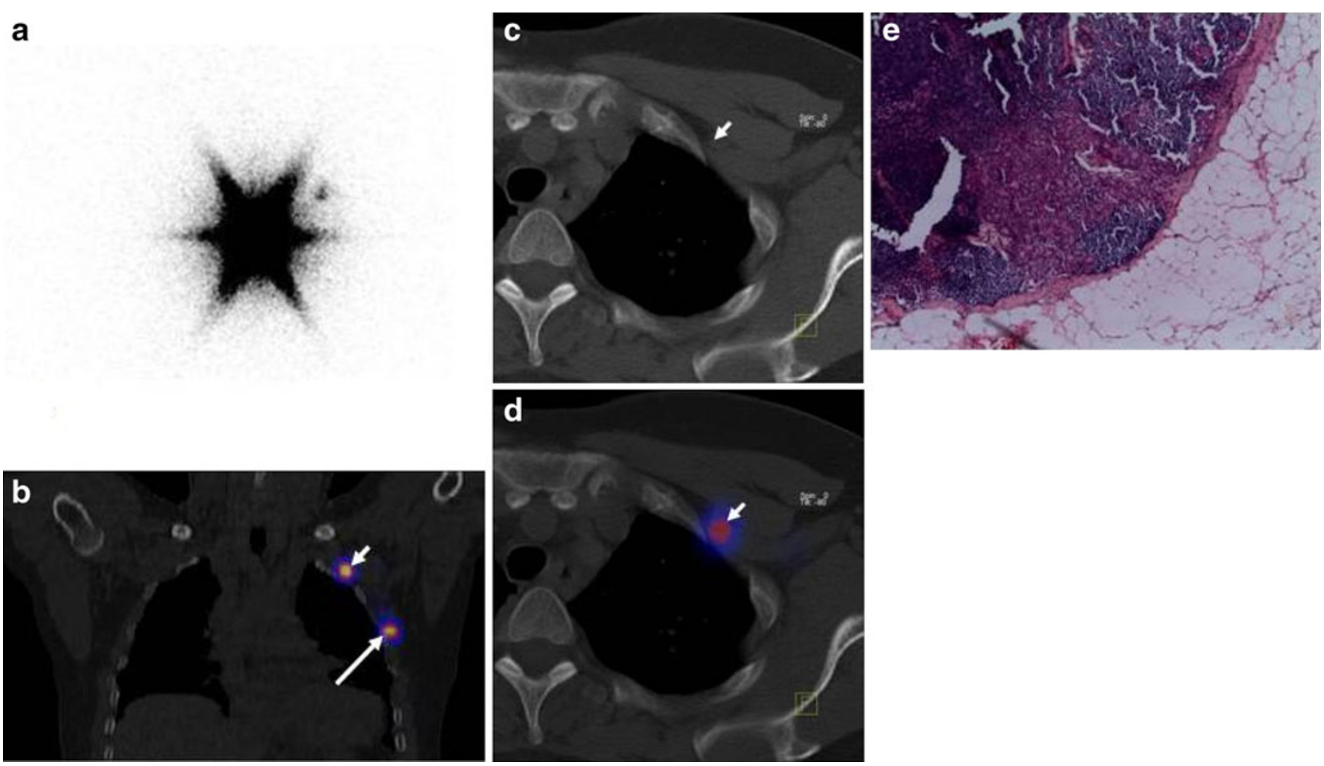

Fig. 5a–e SPECT/CT case acquired on Symbia T2 (Siemens Healthcare). A 54-year-old woman with breast carcinoma (pT1) for SLN mapping. Planar scintigraphy (**a**) detected sentinel lymph node (SLN). Subsequent SPECT/CT shows two SLNs: one in (**b**) typical localisation and (**c**, **d**) one in the upper axilla with 7-mm diameter. Histology proved the second SLN to be malignant (**e**). *Imaging protocol:* 102 MBq ^{99m}Tc-nanocolloid, 0 min pi scintigraphy, 75 min pi SPECT/CT; CT: 100 mAs, 130 kVp, 1-mm/3-mm slices; SPECT: 15 s/image, FBP, no CT-AC. (Courtesy of L.S. Freudenberg, Grevenbroich, Germany)

Most of these earlier publications are from studies performed with Hawkeye systems and, therefore, the addition of clinical CT to SPECT can only enhance the results obtained to date. As the installed base of SPECT/CT systems grows, publications documenting the benefits will no doubt appear in the literature [21, 26].

Improvements and new applications

With routine availability of CT-based attenuation correction SPECT/CT has been widely adopted in favour of SPECT-only imaging. However, unlike PET/CT which has replaced most standalone PET-only systems, SPECT/CT is unlikely to replace all, or even most SPECT. When compared to PET/CT most technical and methodological advances of SPECT, however, are not only available to SPECT/CT users but also to SPECT-only users.

Recently, a number of innovative hardware combinations of SPECT and CT were proposed, giving rise to the idea of disease-specific SPECT/CT imaging. Gambhir et al. [27] and Buechel et al. [28] demonstrated the clinical feasibility and technological benefit of a CdZnTe (CZT)-based SPECT imaging for cardiac applications. While this system is not combined with CT, it illustrates a major leap in SPECT instrumentation that could potentially enter into a new combination of SPECT/CT. The main benefit of CZT over standard scintillator-based SPECT detectors is the much higher energy resolution, which can be explored for dual-isotope imaging. CZT detectors are compact and future CZT SPECT/CT could be more physically integrated. However, today, production costs still limit the wider distribution of these novel SPECT imaging systems.

Already with standard SPECT in combination with CT several groups have demonstrated an increased diagnostic benefit from the availability of co-registered functional and anatomical information in combination with dedicated CT examinations, like angiography [17, 29]. So far these studies have been based on the retrospective alignment of SPECT and CT angiography data acquired on a 64-slice CT. Today, no SPECT/CT system would allow similar type of imaging sequences because of the limited number of CT detector rows (maximum 16, Fig. 3). It is fair to assume that if more SPECT-CT software fusion studies demonstrate the validity of hardware-based acquisitions of SPECT and CTA, then such combinations may well be designed and offered commercially.

In addition to cardiac applications, SPECT/CT can be optimised for orthopaedic imaging. Here, requirements entail fast and sensitive SPECT imaging in combination with high-resolution anatomical background information. As the age distribution of orthopaedic patients is very large, overexposure is a major concern when imaging these patients. Therefore, one vendor has proposed a novel design of SPECT/CT that combines a standard dual-head SPECT system with a cone-beam, flat-panel CT (Fig. 6) [30]. A single, 47-cm axial field-of-view of the SPECT is matched by three contiguous CT acquisitions of 14-cm axial field-of-view flat panel CT, thus allowing the co-axial SPECT/CT imaging range per bed position to be 42 cm.

Other innovations in SPECT/CT are expected from advanced data processing and acquisition (Fig. 7). As with nuclear medicine imaging techniques in general, SPECT describes a count limited imaging situation. Therefore, innovative image reconstruction techniques have been proposed to reduce noise propagation during the recon-

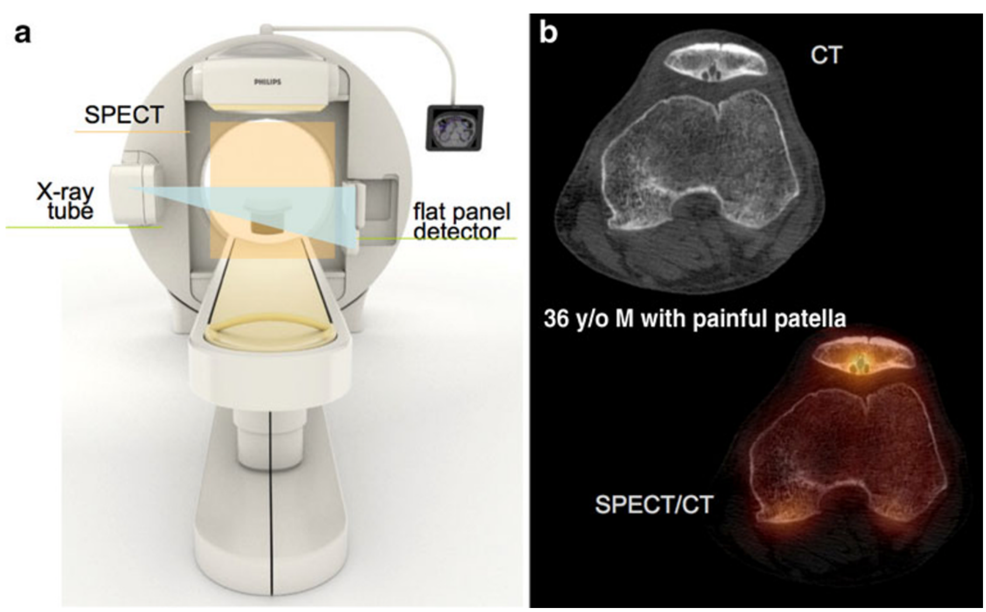

Fig. 6 (**a**) SPECT/CT design with flat panel CT for high-resolution, low-dose CT imaging with a main focus on orthopaedic applications (**b**) and routine attenuation correction. System images courtesy of Philips Healthcare, case study courtesy of T. Krause, Inselspital, Bern, Switzerland

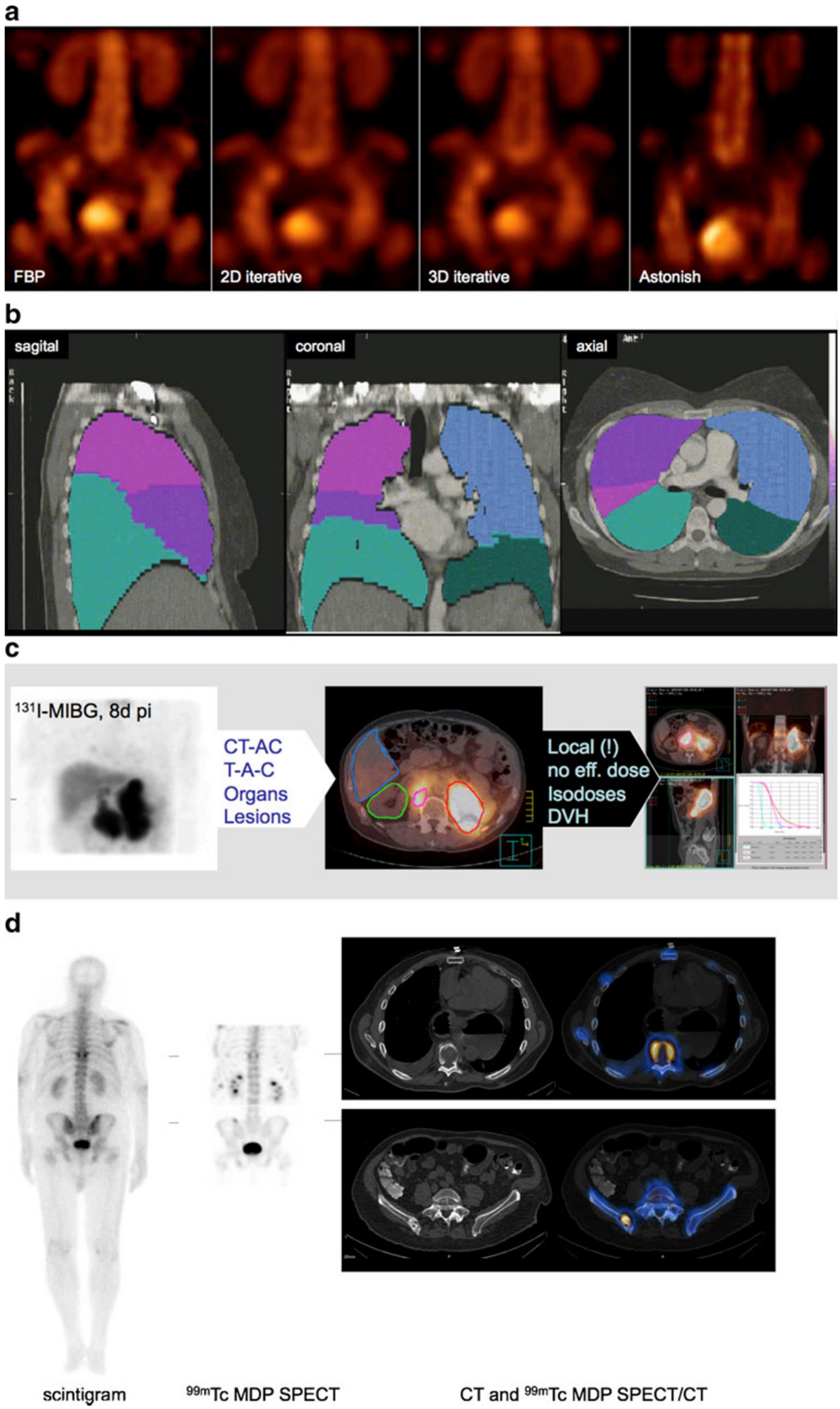

Fig. 7a–d Examples of methodological advances in SPECT/CT imaging and future applications. **a** Advanced three-dimensional (3D) iterative SPECT reconstruction (*Astonish*, Philips Healthcare) incorporating projection-based collimator/COR distance information, collimator resolution, noise reduction and attenuation/scatter correction. (Courtesy of Antonis Kalemis, Philips Healthcare) **b** An example of a segmented CT of the thorax showing the individual lobes of the lung. The colours indicate different regions of interest, which are applied to the co-registered lung image to derive anatomically accurate functional values for ventilation and perfusion from the SPECT lung scan. (Courtesy Dale Bailey, Royal Northshore Hospital, Sydney, Australia) **c** Voxel-based dosimetry from 3D SPECT(/CT). SPECT data following CT-AC are collected for multiple time points. CT-based organ segmentation and SPECT-based lesion segmentation is performed on SPECT/CT images. Local dosimetry is possible and isodose curved and dose-volume histograms can be calculated. (Courtesy of Bernd Schweizer, Philips Healthcare) **d** Whole-body SPECT(/CT): patient with severe back pain with multiple focal uptakes on the scintigram. A contiguous two-bed SPECT/CT acquisition reveals several bone metastases in the spine and pelvis. Multi-bed, or whole-body SPECT/CT helps with the complete restaging of the patient, and is in synchrony with similar referring indications for whole-body PET/CT, which is already widely available. (Courtesy of Ora Israel, Haifa)

struction (Fig. 7a). SPECT/CT images, even when based on low-dose CT acquisitions, provide the ability to anatomically define the fissures separating the lobes of the lungs so that lobar function can be assessed semi-automatically from co-registered V/Q images in patients who are candidates for lung volume reduction surgery (Fig. 7b). Similar approaches are followed when employing SPECT/CT information for image-based dosimetry calculations (Fig. 7c). Finally, Fig. 7d illustrates the potential of multi-bed, whole-body SPECT/CT imaging in oncology. Similar to PET/CT imaging, patients are injected with a single dose of radioactivity for SPECT/CT imaging. Imaging only a single bed position makes suboptimal use of the injected activity. Moreover, in oncology patients, disease can be widely distributed and not covered appropriately with a single bed position of SPECT/CT imaging. Here, a case of a patient with severe back pain with multiple foci of increased tracer uptake on the planar scintogram is shown. A two-bed SPECT/CT acquisition reveals several bone metastases in the spine and pelvis. Multi-bed, or whole-body SPECT/CT helps with the complete restaging of the patient, and is in synchrony with similar referring indications for whole-body PET/CT.

Since the commercial introduction of SPECT/CT in 2004, adoption of the technology has been rapid, particularly for oncology and cardiology. SPECT/CT has benefited from the advances in CT technology. SPECT/CT currently has a smaller installed base than PET/CT, but it is growing. In 2006, there were about 21-million SPECT studies performed in the USA compared with 1.5-million PET and PET/CT studies. The likelihood is that SPECT/CT will continue to grow with expanding applications in cardiology, oncology, infectious disease imaging and others, thereby benefiting from a much wider range of biomarkers and radiopharmaceuticals than clinical PET.

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Conflicts of interest T.B. is president and founder of Switzerland-based cmi-experts GmbH.
D.T. acts as a scientific advisor to cmi-experts of Zurich, Switzerland and RefleXion Medical of Stanford, Calif., USA. He received royalty payments from Siemens Healthcare related to the invention of the PET/CT.
J.C. is co-founder of Momentum Biosciences and Sofie Biosciences, Los Angeles, Calif., USA and serves as an advisor to cmi-experts GmbH, Switzerland.
L.S.F. serves as an advisor to cmi-experts of Zurich, Switzerland and has received speaker fees from Siemens, Philips and Genzyme.

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